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ORIGINAL ARTICLE

Multi-detector CT perfusion as a diagnostic imaging modality to evaluate local therapy of hepatocellular carcinoma

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KEYWORDS

HCC, hepatocellular carcinoma;
RFA, radiofrequency ablation;
TACE, trans-arterial chemoembolization;
TDC, time density curve;
CTP, volume perfusion MDCT

Abstract *Objective:* To evaluate MDCT perfusion role in HCC local therapy response.
Patients and methods: Post radiofrequency ablation and trans-arterial chemoembolization 14 (88%) male and 2 (12%) female HCC patients; with the mean age, 55.75 ± 10.6 years underwent follow-up hepatic CT perfusion. The hepatic arterial and portal venous perfusions (HAP and HPP, ml/min/100 ml) and hepatic perfusion index (HPI%) were indicated using the color coded maps to assess the effects of local therapy on hepatic perfusion values.
Results: The post local treatment CTP of the recurrent tumor confirmed relative increased HAP and HPI and reduced PVP relative to the background values of the cirrhotic hepatic parenchyma. The recurrent HCC post-treatment CTP including HAP is 71 ± 12.19, the PVP is 25.5 ± 8.66 and HPI is 52.5 ± 11.9. The post local-treatment CTP of the necrosis confirmed relative decreased HAP and HPI and increased PVP. The post-treatment necrosis CTP including HAP is 23 ± 10.39, the PVP is 34.75 ± 11.5 and HPI is 29 ± 16.51. The CTP sensitivity is 75%, specificity 50% and *P*-value < 0.05.
Conclusion: CTP is a promising non-invasive technique assessing the efficacy, predicting early response to local treatment therapies and monitoring tumor recurrence. It assesses the degree of post therapy tumor perfusion especially the degree of arterialization.

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide accounting for 90% of primary malignant neoplasm of the liver (1). It is responsible for more than 500,000 deaths every year globally (2). Limitations of traditional imaging response criteria, such as World Health Organization (WHO) criteria or Response Evaluation Criteria in Solid Tumors (RECIST) for evaluating targeted therapies have been widely established (3). Recently, tumor density measurement and tissue biopsy coupled with micro vessel density (MVD) assessment have been explored as potential new methods for

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assessing response to therapy (2). However, the biopsies could be limited due to prevalence of underlying cirrhosis and coagulopathy (1) (see Fig. 1–3).

Volume Perfusion MDCT (CTP) is a promising method for calculating hepatic arterial and portal blood flow, including microcirculation, using a color-encoded display of parameters obtained from the liver time density curve, with iodine contrast agent (3).

CTP allows for quantification of perfusion in absolute units at high spatial resolution. This method is reportedly useful for evaluation of severity of hepatic fibrosis associated, assessment of hepatic tumor perfusion and prediction of tumor response to therapies (4). Wang et al. (5) and Ng et al. (6) reported improved monitoring of hepatic perfusion changes after radiological interventions.

However, some problems remain with using CTP, such as long breath holding for portal flow measurement, limited craniocaudal scan range, separation of arterial and portal blood flow, standardization of analytic methods, and unknown effects of extrahepatic factors (4).

This study was aimed to evaluate role of CTP in HCC local therapy response.

2. Patients and methods

2.1. Patients

Between February 2014 and November 2015, a total of 16 patients were subjected to this study, and out of them 14 (88%) were male patients and 2 (12%) were female, with the mean age, 55.75 ± 10.6 years and age between 41 and 72 years. This retrospective study monitored the patients with HCC undergoing local treatment in the terms of RFA and TACE. The local Institutional Review Board approved the study and all patients gave their written consent.

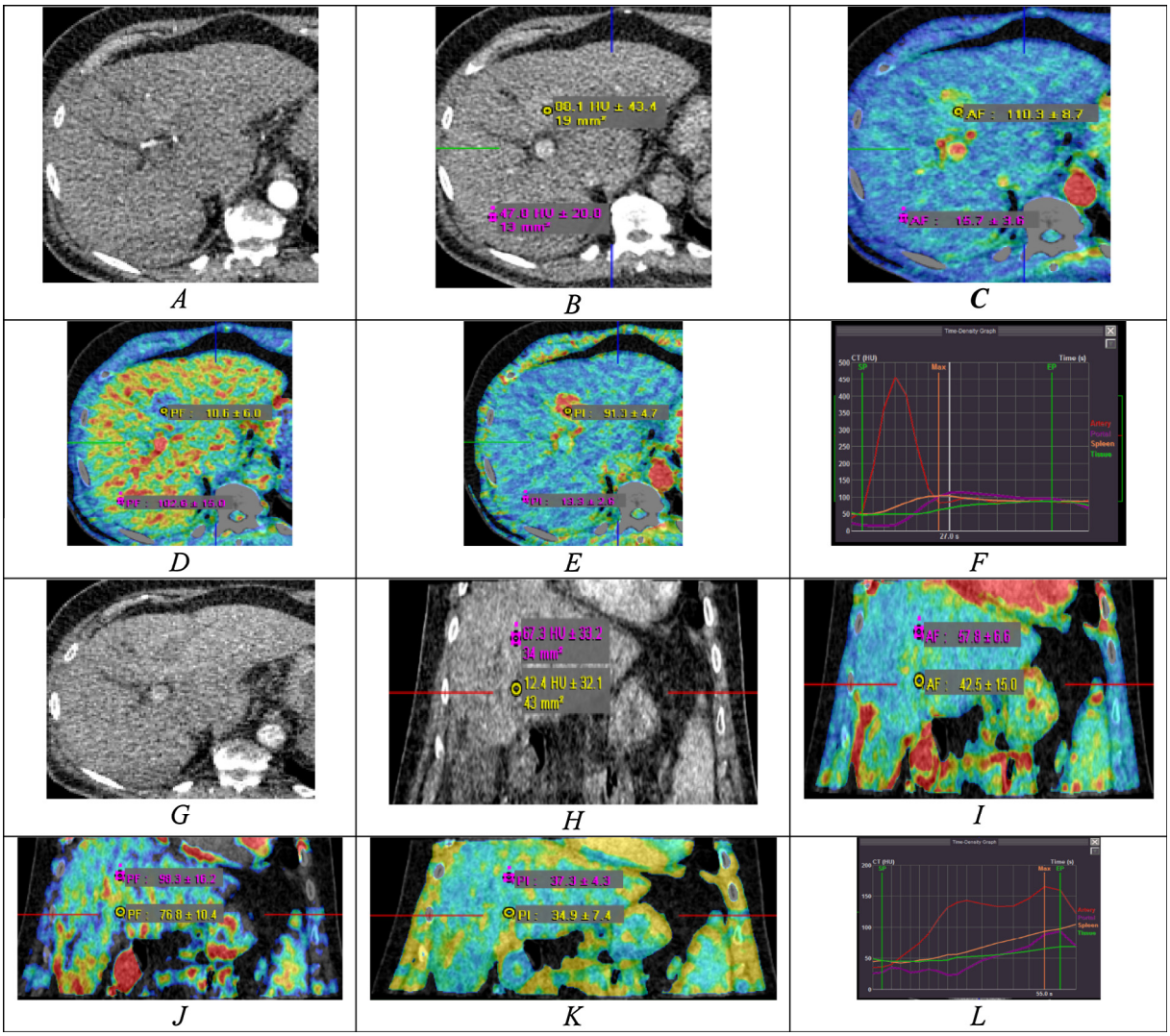

Fig. 1 70 years old Male patient with elevated AFP, and left hepatic lobe lateral segment ill-defined focal HCC (A, B, C, D, E and F). Follow-up Post RFA Triphasic CT and CTP revealed recurrent eccentric tumor activity and at the superior extent of the post RFA coagulative necrosis (G, H, I, J, K and L). CTP of the tumor confirmed relative increased HAP/AF and HPI/PI as well as reduced PVP/PF. CTP of the post RFA coagulative necrosis revealed relative decreased HAP/AF and HPI/PI as well as increased PVP/PF.

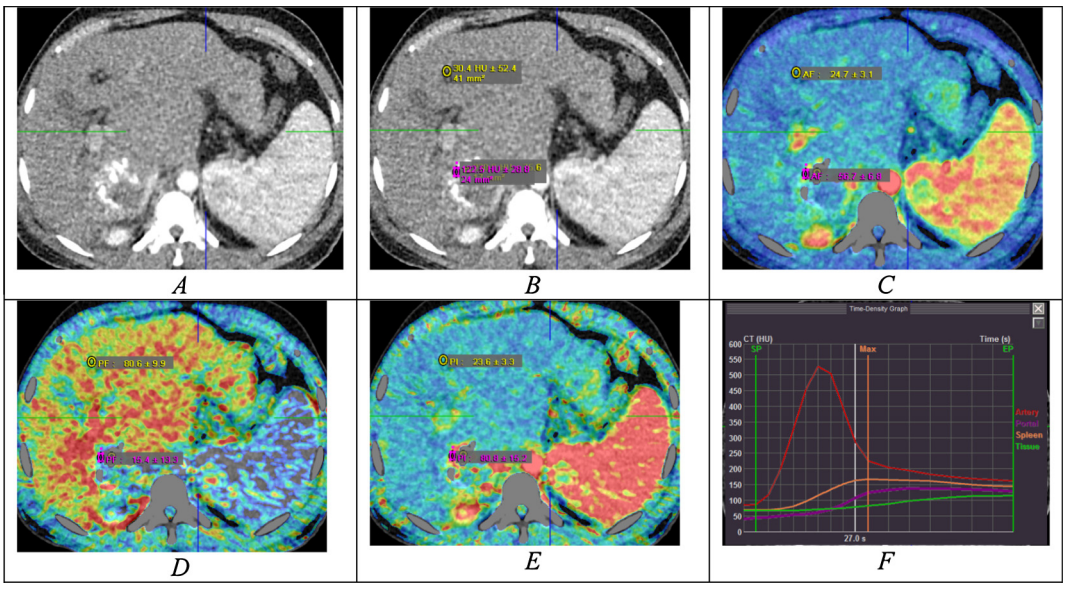

Fig. 2 72 years old Male patient with elevated AFP, and right hepatic lobe segment 7 focal HCC underwent TACE. Follow-up Triphasic CT (A and B) and CTP (C, D, E and F) revealed recurrent tumor activity. CTP of the tumor confirmed relative increased HAP/AF and HPI/PI as well as reduced PVP/PF.

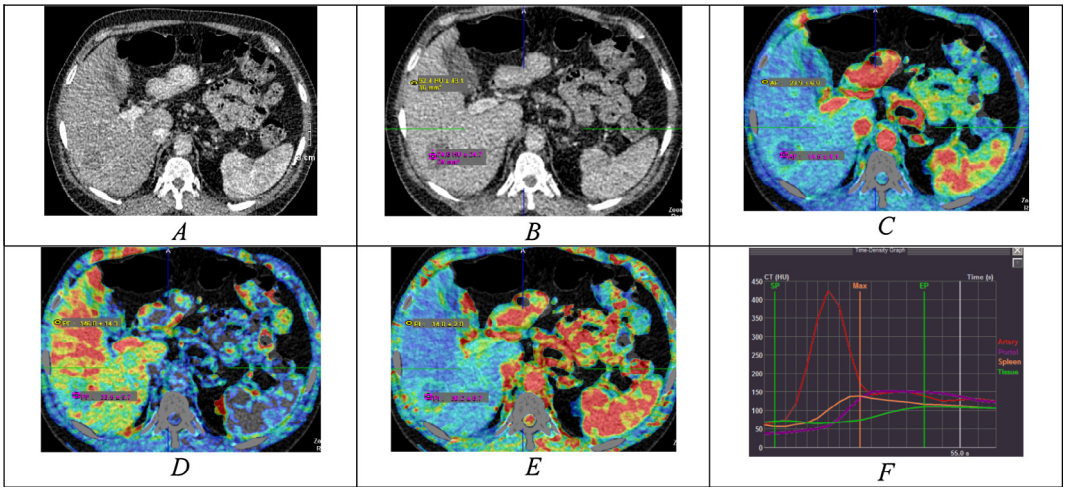

Fig. 3 54 years old Male patient with right hepatic lobe segment 7 focal HCC underwent RFA. Follow-up Triphasic CT (A and B) and CTP (C, D, E and F) revealed post RFA coagulative necrosis with relative decreased HAP/AF HPI/PI and increased PVP/PF.

Inclusion criteria for this study were liver cirrhosis, with pre and post TACE or RFA. Suspected or confirmed HCC histologically was proven in (7) patients or based on imaging features in 8 (50%) patients together with elevated serum alpha feto proteine level >200 in 10 (62.5%) patients. Exclusion criteria were contraindication of IV contrast media administration including elevated serum creatinine and contrast allergy. Patients were weighed ($\geqslant 130$ kg) because of machine weight limit and for better image quality demonstration.

All patients had liver cirrhosis according to Child Pugh criteria, and they are Child A. Underlying cause of cirrhosis in the patients was Hepatitis C-virus. None of our patients give history of alcohol intake or proved to have Hepatitis B-virus infection.

2.2. MDCT perfusion (CTP) imaging protocol

All examinations were performed in Police Authority Nasr City Hospital using 320-row CT scanner (Aquilion ONE 320-MDCT, Toshiba medical systems corporation, Japan). The CT protocol consisted of a non-enhanced abdominal low-dose CT (40 mAs, 100 kV) to localize the porta hepatis. Liver CTP parameters were as follows: (80 kV, 100 mAs). At first test bolus technique was performed and subsequently the perfusion measurements were started accordingly. A 50 mL of non-ionic water soluble contrast media was injected followed by a saline flush.

Table 1 Triphasic CT findings.

	Conventional triphasic CT		Paired diff.		Paired sample *t*-test	
	Mean	±SD	Mean	±SD	*t*	*P*-value
Liver density (cirrhosis)	64.00	12.54				
Tumor density (pre RFA/TACE)	122.75	41.33	−58.75	42.64	−3.897	**0.006**
Tumor density (Recurrence)	98.00	39.68	−34.00	45.46	−2.115	0.072
Tumor necrosis density	27.00	3.46	28.00	12.70	4.409	**0.022**
Tumor size (pre-treatment)	4.50	1.20				
Recurrent tumor size (post treatment)	3.25	0.89	1.25	1.39	2.546	**0.038**

2.3. Image analysis

Axial and coronal reformatted images were obtained for perfusion analysis using Vitrea external workstation. Regions of interest (ROI) were placed in the abdominal aorta at the level of the celiac axis for the arterial input function (AIF). Additionally ROIs in the portal vein, spleen and tumor were placed to generate time-density curves (TDC). Subsequently, dual-input single compartment model method was used for separate calculation of arterial (HAP/AF) and portal-venous (PVP/PF) blood flow to the liver and tumor. HAP and PVP values are given in (ml/100 mL) tissue/minute and HPI (%) is indicated using the color coded maps.

2.3.1. Statistical analysis

Data were analyzed using Statistical Program for Social Science (SPSS) version 22.0. Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done:

Independent-samples *t*-test of significance was used when comparing between two means.

- Chi-square (X2) test of significance was used in order to compare proportions between two qualitative parameters.
- Receiver operating characteristic (ROC curve) analysis was used to find out the overall predictivity of parameter in and to find out the best cutoff value with detection of sensitivity and specificity at this cutoff value.
  1. Sensitivity = (true +ve)/[(true +ve) + (false −ve)].
  2. Specificity = (true −ve)/[(true −ve) + (false +ve)].
  3. PPV = (true +ve)/[(true +ve) + (false +ve)].
  4. NPV = (true −ve)/[(true −ve) + (false −ve)].

- Probability (*P*-value)
  1. *P*-value < 0.05 was considered significant.
  2. *P*-value < 0.001 was considered as highly significant.
  3. *P*-value > 0.05 was considered insignificant.

3. Results

The triphasic CT and CTP were performed pre and post treatment including RFA in 12 (75%) patients and TACE in 4 (25%) patients, for evaluation of morphological triphasic CT and functional CTP criteria of HCC (Table 1).

The pre-treatment triphasic CT findings include Hepatic cirrhosis parenchyma density (64 ± 12.54 HU), pre-RFA/TACE tumor density (122.75 ± 41.33 HU), and tumor size (4.5 ± 1.2 cm). The tumor was visible in 8 (50%) patients. It is ill-defined in the other 8 (50%) patients (Table 1).

The pre-treatment CTP of tumor confirmed increased HAP and HPI and reduced PVP relative to the cirrhotic parenchyma values. The pre-treatment CTP finding of the cirrhotic parenchyma including HAP is 18.5 ± 3.74, the PVP is 94.75 ± 15.52 and HPI is 16.75 ± 4.03. The HCC pre-treatment HAP is 104 ± 10.28, the PVP is 13.25 ± 10.78 and HPI is 91.50 ± 7.87 (Table 2).

The post RFA/TACE Triphasic CT findings include recurrent tumor density (98 ± 39.68 HU) and recurrent tumor size (3.25 ± 0.89 cm). It is visible in 6 (37.5%) patients. In addition the post treatment necrosis density is 37.2 ± 20.2.

The post local-treatment CTP of the recurrent tumor confirmed relative increased HAP and HPI and reduced PVP relative to the background values of the cirrhotic hepatic parenchyma. The recurrent HCC post-treatment CTP including HAP is 71 ± 12.19, the PVP is 25.5 ± 8.66 and HPI is 52.5 ± 11.9. The post local-treatment CTP of the necrosis confirmed relative decreased HAP and HPI and increased PVP. The post-treatment necrosis CTP including HAP is 23 ± 10.39, the PVP is 34.75 ± 11.5 and HPI is 29 ± 16.51.

The Triphasic CT scanning sensitivity (40%), specificity (33.3%), positive (50%) and negative (25%) predictive values as well as the accuracy (37.5%) and *P*-value (>0.05). The CTP sensitivity (75%), specificity (50%), positive (60%) and negative (66.7%) predictive values as well as the accuracy (62.5%) and *P*-value (<0.05) (Table 3).

4. Discussion

The liver is the most challenging organ for perfusion imaging, due to its unique dual vascular supply (8) and considerable respiratory motion (7). Our study not agrees with Spira et al. (7), who reported that the liver is probably the most challenging organ for CTP measurement and interpretation due to considerable diaphragmatic movement during breathing, as the motion correction and the application of filters allow reconstruction of good-quality images even with free-breathing of the patient during scanning. Triphasic CT is the main diagnostic tool in tumor evaluation, including diagnosis, staging, or monitoring of therapies because of the relatively low cost and wide availability. CTP may augment standard therapeutic assessment in clinical trials and in the clinical environment. By use of functional imaging techniques to assess the response to therapy, it would be possible to achieve earlier discrimination between responders and non-responders (8).

Table 2 CTP HCC findings.

	CT Perfusion		Paired diff.		Paired sample *t*-test	
	Mean	±SD	Mean	±SD	*t*	*P*-value
HAP (Cirrhosis)	18.50	3.74				
HAP (pre RFA/TACE)	104.00	10.28	−85.50	10.73	−22.54	**<0.001**
HAP (Tumor recurrence)	71.00	12.19	−54.00	13.83	−7.81	**0.004**
HAP (Tumor necrosis)	23.00	10.39	25.75	21.93	3.32	**0.013**
PVP (Cirrhosis)	94.75	15.52				
PVP (pre RFA/TACE)	13.25	10.78	81.50	25.42	9.07	**<0.001**
PVP (Tumor recurrence)	25.50	8.66	83.00	1.15	143.76	**<0.001**
PVP (Tumor necrosis)	34.75	11.50	62.50	52.01	3.40	**0.011**
HPI (Cirrhosis)	16.75	4.03				
HPI (pre RFA/TACE)	91.50	7.87	−74.75	11.32	−18.67	**<0.001**
HPI (Tumor recurrence)	52.50	11.90	−38.50	13.03	−5.91	**0.010**
HPI (Tumor necrosis)	29.00	16.51	5.25	17.03	0.87	0.412

Table 3 Triphasic CT and CTP parameters.

	Treatment conventional triphasic CT	Treatment necrosis CT perfusion
Positive	8	12
Negative	8	4
Sensitivity	40%	75%
Specificity	33.3%	50%
+PV	50%	60%
−PV	25%	66.67%
Accuracy	37.5%	62.5%
P-value	>0.05 (NS)	<0.05 (S)

Our results showed that recurrent HCC was ill defined in 8 (50%) of patients at pre-treatment triphasic CT scanning. These results are explained by Takayasu et al. (9), who reported that 44% of early HCCs could not be detected due to iso-attenuation in triphasic CT.

The liver diseases show alterations of vascular physiology which are easily recognized via CTP. CTP is defined as "real" blood flow through a volume of tissue per time and therefore constitutes a very different parameter from the well-known concept of blood velocity, which is used for the evaluation of flow dynamics in large vessels. CTP measures temporal changes in tissue density after IV contrast injection using repeated CT scans of the volume being analyzed. Thus density measurements include contrast material contained in the intra as well as the extra vascular space (7).

The liver is the most challenging organ for CTP interpretation due to considerable respiratory movement and dual blood supply. Importantly separate calculation of HAP and PVP by placement of ROIs in PV and spleen is possible due to simultaneous perfusion of both organs via hepatic and splenic arteries. In focal liver lesions CTP facilitates the tumor vascularity and permeability analysis. This overcomes the limitations of slice-dependent assessment and may prove beneficial in therapy monitoring of focal tumors (10).

Importantly, CTP enables distinction of tumor thrombus from non-vascularized thrombosis. CTP aids in the detection characterization as well as response assessment of tumors to therapy, including therapy-related complications (e.g. hemorrhage, liver parenchymal necrosis) (7).

CTP has been used for early identification of tumor recurrence after regional image-guided therapies of HCC. Our results agree with Mahnken et al. (11) who reported the usefulness of quantitative volumetric arterial enhancement fraction color mapping for the early detection of recurrent tumor after RFA. They observed that the tumor arterial perfusion values were significantly higher when compared with liver parenchyma.

Our results demonstrated that the post treatment Triphasic CT findings include recurrent tumor density (98 ± 39.68 HU) and recurrent tumor size (3.25 + 0.89). It is visible in 6 (37.5%) patients. In addition the post treatment necrosis density is 27 ± 3.46. The post local-treatment CTP of the recurrent tumor confirmed relative increased HAP and HPI and reduced PVP relative to the background values of the cirrhotic hepatic parenchyma. The recurrent HCC post-treatment CTP including HAP is 71 ± 12.19, the PVP is 25.5 ± 8.66 and HPI is 52.5 ± 11.9. The post local-treatment CTP of the necrosis confirmed relative decreased HAP and HPI and increased PVP. The post-treatment necrosis CTP including HAP is 23 ± 10.39, the PVP is 34.75 ± 11.5 and HPI is 29 ± 16.51.

In addition, our results are in partial agreement with Meijerink et al. (12), who reported that marginal lesions with high HAP (>50 mL/min/100 g) and low hepatic portal perfusion (<10 mL/min/100 g) represented recurrent tumor tissue after RFA with an increased risk for local RFA–site tumor recurrence. Furthermore, areas of recurrent tumors on CTP images were well matched with hot spots on PET/CT images.

Ippolito et al. (13) and Choi et al. (14) reported that CTP parameters obtained 1 week after TACE did not help predict future recurrence. The recurrence eventually occurred at 4 weeks after TACE. The recurrent HCC within TACE-treated areas had significantly higher HAP, and HPI than the lipiodolized area or the cirrhotic parenchyma.

Early identification of tumor recurrence around RFA defect or lipiodolized nodule is sometimes challenging with conventional CT because tumor recurrence around RFA defect can be confused with reactive hyperemia around RFA area and because HCC recurrence around lipiodolized nodule can be obscured by beam hardening artifacts that occurred due to high attenuation of accumulated lipiodol. CTP may play an important role in these aspects, being noteworthy in patient management. However, further studies with larger study populations are again needed to assess the role of CT perfusion in diagnosing tumor recurrence early (15).

This study has several limitations. First, our study suffers from a relative short term study and limited number of

patients. Second, there was histological proof of HCC in 8 (50%) patients due to the presence of elevated serum AFP level >200 in 10 (62%) patients, who were enrolled as a result of typical imaging findings in a background of cirrhotic liver. This inclusion criteria is in partial agreement with Kaufmann et al. (1), who stated that they include newly occurred liver lesions presenting typical imaging findings (wash-in and/or wash-out kinetics) suggestive for e.g. early HCC as their ethic board approval included only HCC-typical lesions amenable for local therapy. Third, we did not document the radiation exposure dose; however, the radiation exposure in our research might be increased. This is confirmed by Kaufmann et al. (1) who stated that mean radiation exposure for liver perfusion measurements was 7 mSv. It is explained by Wang et al. (5) who reported that the wide craniocaudal scan range and relative large number of scans increased volume computed tomographic dose index. The radiation dose can be lowered in the future combining with further optimized perfusion imaging protocols. Fourth, we only applied dual-input single compartment mode to calculate perfusion values and we are not using deconvolution or maximal slope methods. However this is not consistent with Wang et al. (5) and Kanda et al. (4) who used maximal slope mode, due to the relative simple underlying principle; is the dominate one in the field of liver perfusion measurement and is widely applied in many studies. Further studies are required to confirm our findings and to better understand segmental variances of hepatic parenchyma, in both normal and pathological conditions, Wang et al. (5).

Conclusion

Our study proved that CTP is a promising technique assessing the efficacy, predicting early response to local therapies and monitoring tumor recurrence. It assesses the degree of post therapy tumor perfusion especially its arterialization. It is adjunct to hepatic conventional triphasic imaging techniques. It enables distinction of tumor thrombus from non-vascularized thrombosis.

Conflict of interest

The authors declare that there are no conflict of interests.

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